SECTION 2. RISK CHARACTERIZATION

EPA risk assessment principles and practices draw on many sources. The environmental laws administered by EPA, the National Research Council's 1983 report on risk assessment (1), the Agency's Risk Assessment Guidelines (3), and various program-specific guidance (e.g., the Risk Assessment Guidance for Superfund) are obvious sources. Twenty years of EPA experience in developing, defending, and enforcing risk assessment-based regulation is another. Together these various sources stress the importance of a clear explanation of Agency processes for evaluating hazard, dose-response, exposure, and other data that provide the scientific foundation for characterizing risk.

This section focuses on two requirements for full characterization of risk. First, the characterization must address qualitative and quantitative features of the assessment. Second, it must identify any important uncertainties in the assessment as part of a discussion on confidence in the assessment.

This emphasis on a full description of all elements of the assessment draws attention to the importance of the qualitative as well as the quantitative dimensions of the assessment. The 1983 NRC report carefully distinguished qualitative risk assessment from quantitative assessments, preferring risk statements that are not strictly numerical.

> The term <u>risk assessment</u> is often given narrower and broader meanings than we have adopted here. For some observers, the term is synonymous with <u>quantitative</u>

> risk assessment and emphasizes reliance on numerical results. Our broader definition includes quantification, but also includes qualitative expressions of risk. Quantitative estimates of risk are not always feasible, and they may be eschewed by agencies for policy reasons. (Emphasis in original) (1)

More recently, an Ad Hoc Study Group (with represenatives from EPA, HHS, and the private sector) on Risk Presentation reinforced and expanded upon these principles by specifying several "attributes" for risk characterization.

> 1. The major components of risk (hazard identification, dose-response, and exposure assessment) are presented in summary statements, along with quantitative estimates of risk, to give a combined and integrated view of the evidence.
>
> 2. The report clearly identifies key assumptions, their rationale, and the extent of scientific consensus; the uncertainties thus accepted; and the effect of reasonable alternative assumptions on conclusions and estimates.
>
> 3. The report outlines specific ongoing or potential research projects that would probably clarify significantly the extent of **uncertainty** in the risk estimation. . . . (4)

Particularly critical to full characterization of risk is a frank and open discussion of the uncertainty in the overall assessment and in each of its components. The uncertainty statement is important for several reasons.

- Information from different sources carries different kinds of uncertainty and knowledge of these differences is important when uncertainties are combined for characterizing risk.
- Decisions must be made on expending resources to acquire additional information to reduce the uncertainties.

- A clear and explicit statement of the implications and limitations of a risk assessment requires a clear and explicit statement of related uncertainties.

- Uncertainty analysis gives the decision-maker a better understanding of the implications and limitations of the assessments.

A discussion of uncertainty requires comment on such issues as the quality and quantity of available data, gaps in the data base for specific chemicals, incomplete understanding of general biological phenomena, and scientific judgments or science policy positions that were employed to bridge information gaps.

In short, broad agreement exists on the importance of a full picture of risk, particularly including a statement of confidence in the assessment and that the uncertainties are within reason. This section discusses information content and uncertainty aspects of risk characterization, while Section 3 discusses various descriptors used in risk characterization.

1. The risk assessment process calls for characterizing risk as a combination of qualitative information, quantitative information, and information regarding uncertainties.

Risk assessment is based on a series of questions that the assessor asks about the data and the implications of the data for human risk. Each question calls for analysis and interpretation of the available studies, selection of the data that are most scientifically reliable and most relevant to the problem at hand, and scientific conclusions regarding the question presented. As suggested below, because the questions and analyses are complex, a complete characterization includes several different kinds of information, carefully selected for reliability and relevance.

a. Hazard Identification -- What do we know about the capacity of an environmental agent for causing cancer (or other adverse effects) in laboratory animals and in humans?

Hazard identification is a qualitative description based on factors such as the kind and quality of data on humans or laboratory animals, the availability of ancillary information (e.g., structure-activity analysis, genetic toxicity, pharmacokinetics) from other studies, and the weight-of-the evidence from all of these data sources. For example, to develop this description, the issues addressed include:

1. the nature, reliability, and consistency of the particular studies in humans and in laboratory animals;

2. the available information on the mechanistic basis for activity; and

3. experimental animal responses and their relevance to human outcomes.

These issues make clear that the task of hazard

identification is characterized by describing the full range of available information and the implications of that information for human health.

b. Dose-Response Assessment -- What do we know about the biological mechanisms and dose-response relationships underlying any effects observed in the laboratory or epidemiology studies providing data for the assessment?

The dose-response assessment examines quantitative relationships between exposure (or dose) and effects in the studies used to identify and define effects of concern. This information is later used along with "real world" exposure information (see below) to develop estimates of the likelihood of adverse effects in populations potentially at risk.

Methods for establishing dose-response relationships often depend on various assumptions used in lieu of a complete data base and the method chosen can strongly influence the overall assessment. This relationship means that careful attention to the choice of a high-to-low dose extrapolation procedure is very important. As a result, an assessor who is characterizing a dose-response relationship considers several key issues:

1. relationship between extrapolation models selected and available information on biological mechanisms;

2. how appropriate data sets were selected from those that show the range of possible potencies both in laboratory animals and humans;

3. basis for selecting interspecies dose scaling factors to account for scaling doses from experimental animals to humans; and

4. correspondence between the expected route(s) of exposure and the exposure route(s) utilized in the hazard studies, as well as the interrelationships of potential effects from different exposure routes.

EPA's Integrated Risk Information System (IRIS) is a primary source of this information. IRIS includes data summaries representing Agency consensus on specific chemicals, based on a careful review of the scientific issues listed above. For specific risk assessments based on data in IRIS and on other sources, risk assessors should carefully review the information presented, emphasizing confidence in the database and uncertainties (see subsection d below). The IRIS statement of confidence should be included as part of the risk characterization for hazard and dose-response information.

c. Exposure Assessment -- What do we know about the paths, patterns, and magnitudes of human exposure and numbers of persons likely to be exposed?

The exposure assessment examines a wide range of exposure parameters pertaining to the "real world" environmental scenarios of people who may be exposed to the agent under study. The data considered for the exposure assessment range from monitoring studies of chemical concentrations in environmental media, food, and other materials to information on activity patterns of different population subgroups. An assessor who characterizes exposure should address several issues.

1. The basis for the values and input parameters used for each exposure scenario. If based on data, information on the quality, purpose, and representativeness of the database is needed. If based on assumptions, the source and general logic used to develop the assumption (e.g., monitoring, modeling, analogy, professional judgment) should be described.

2. The major factor or factors (e.g., concentration, body uptake, duration/frequency of exposure) thought to account for the greatest uncertainty in the exposure estimate, due either to sensitivity or lack of data.

3. The link of the exposure information to the risk descriptors discussed in Section 3 of this Appendix. This issue includes the conservatism or non-conservatism of the scenarios, as indicated by the choice of descriptors.

In summary, confidence in the information used to characterize risk is variable, with the result that risk characterization requires a statement regarding the assessor's confidence in each aspect of the assessment.

d. Risk Characterization -- What do other assessors, decision-makers, and the public need to know about the primary conclusions and assumptions, and about the balance between confidence and uncertainty in the assessment?

In the risk characterization, conclusions about hazard and dose response are integrated with those from the exposure assessment. In addition, confidence about these conclusions, including information about the uncertainties associated with the final risk summary, is highlighted. As summarized below, the characterization integrates all of the preceding information to communicate the overall meaning of, and confidence in, the hazard, exposure, and risk conclusions.

Generally, risk assessments carry two categories of uncertainty, and each merits consideration. Measurement uncertainty refers to the usual variance that accompanies scientific measurements (such as the range around an exposure estimate) and reflects the accumulated variances around the individual measured values used to develop the estimate. A

different kind of uncertainty stems from data gaps -- that is, information needed to complete the data base for the assessment. Often, the data gap is broad, such as the absence of information on the effects of exposure to a chemical on humans or on the biological mechanism of action of an agent.

The degree to which confidence and uncertainty in each of these areas is addressed depends largely on the scope of the assessment and the resources available. For example, the Agency does not expect an assessment to evaluate and assess every conceivable exposure scenario for every possible pollutant, to examine all susceptible populations potentially at risk, or to characterize every possible environmental scenario to determine the cause and effect relationships between exposure to pollutants and adverse health effects. Rather, the uncertainty analysis should reflect the type and complexity of the risk assessment, with the level of effort for analysis and discussion of uncertainty corresponding to the level of effort for the assessment. Some sources of confidence and of uncertainty are described below.

Often risk assessors and managers simplify discussion of risk issues by speaking only of the numerical components of an assessment. That is, they refer to the weight-of-evidence, unit risk, the risk-specific dose or the q1* for cancer risk, and the RfD/RfC for health effects other than cancer, to the exclusion of other information bearing on the risk case. However, since every assessment carries uncertainties, a simplified numerical

presentation of risk is always incomplete and often misleading. For this reason, the NRC (1) and EPA risk assessment guidelines (2) call for "characterizing" risk to include qualitative information, a related numerical risk estimate and a discussion of uncertainties, limitations, and assumptions.

Qualitative information on methodology, alternative interpretations, and working assumptions is an important component of risk characterization. For example, specifying that animal studies rather than human studies were used in an assessment tells others that the risk estimate is based on assumptions about human response to a particular chemical rather than human data. Information that human exposure estimates are based on the subjects' presence in the vicinity of a chemical accident rather than tissue measurements defines known and unknown aspects of the exposure component of the study.

Qualitative descriptions of this kind provide crucial information that augments understanding of numerical risk estimates. Uncertainties such as these are expected in scientific studies and in any risk assessment based on these studies. Such uncertainties do not reduce the validity of the assessment. Rather, they are highlighted along with other important risk assessment conclusions to inform others fully on the results of the assessment.

2. Well-balanced risk characterization presents information for other risk assessors, EPA decision-makers, and the public regarding the strengths and limitations of the assessment.

The risk assessment process calls for identifying and highlighting significant risk conclusions and related uncertainties partly to assure full communication among risk assessors and partly to assure that decision-makers are fully informed. Issues are identified by acknowledging noteworthy qualitative and quantitative factors that make a difference in the overall assessment of hazard and risk, and hence in the ultimate regulatory decision.

The key word is "noteworthy": information that significantly influences the analysis is retained -- that is, noted -- in all future presentations of the risk assessment and in the related decision. Uncertainties and assumptions that strongly influence confidence in the risk estimate require special attention.

As discussed earlier, two major sources of uncertainty are variability in the factors upon which estimates are based and the existence of fundamental data gaps. This distinction is relevant for some aspects of the risk characterization. For example, the central tendency and high end individual exposure estimates are intended to capture the variability in exposure, lifestyles, and other factors that lead to a distribution of risk across a population. Key considerations underlying these risk estimates should be fully described. In contrast, scientific assumptions are used to bridge knowledge gaps such as the use of scaling or

extrapolation factors and the use of a particular upper confidence limit around a dose-response estimate. Such assumptions need to be discussed separately, along with the implications of using alternative assumptions.

For users of the assessment and others who rely on the assessment, numerical estimates should never be separated from the descriptive information that is integral to risk characterization. All documents and presentations should include both; in short reports, this information is abbreviated but never omitted.

For decision-makers, a complete characterization (key descriptive elements along with numerical estimates) should be retained in all discussions and papers relating to an assessment used in decision-making. Fully visible information assures that important features of the assessment are immediately available at each level of decision-making for evaluating whether risks are acceptable or unreasonable. In short, differences in assumptions and uncertainties, coupled with non-scientific considerations called for in various environmental statutes, can clearly lead to different risk management decisions in cases with ostensibly identical quantitative risks; i.e., the "number" alone does not determine the decision.

Consideration of alternative approaches involves examining selected plausible options for addressing a given uncertainty. The key words are "selected" and "plausible;" listing all options, regardless of their merits would be superfluous.

Generators of the assessment should outline the strengths and weaknesses of each alternative approach and as appropriate, estimates of central tendency and variability (e.g., mean, percentiles, range, variance.)

Describing the option chosen involves several statements.

1. A rationale for the choice.
2. Effects of option selected on the assessment.
3. Comparison with other plausible options.
4. Potential impacts of new research (on-going, potential near-term and/or long-term studies).

For users of the assessment, giving attention to uncertainties in all decisions and discussions involving the assessment, and preserving the statement of confidence in all presentations is important. For decision-makers, understanding the effect of the uncertainties on the overall assessment and explaining the influence of the uncertainties on the regulatory decision.